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(57) Abstract

A solid preparation for a substantially immediate release of an active agent with low or very low solubility, which contains the active agent dissolved in a solubilizer, said dissolved active agent being contained in solid particles which are agglomerated into a system of agglomerated particles which is not a matrix forming system.

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HIGH RELEASE SOLID PREPARATION, PREPARATION AND USE THEREOF

THE STATE OF THE ART

The present invention relates to a formulation of pellets or solid particles having a specific release, namely a very high release rate of active agents known as being poorly soluble.

In order to increase, the solubility or bioavailability of an active agent, it has been proposed to transform the active agent into its amorphous state. For example, US 4,127,647 discloses the preparation of a solution of a macrolide, a solvent such as trichloroethane and chloroform, and a stabilizing substance such as hydroxypropylmethyl cellulose, and the spray drying of said solution at a temperature of 100-130°C, whereby the solvent is evaporated and removed. The obtained amorphous product is thus free from solvent.

The skilled art worker did not make many attempts to produce pellets with a high release rate, as pellets are mainly produced in oral controlled dosage form.

The man skilled in the art has made searches and developments of pellets with slow or extended release properties.

For example, EP-A-0249587 teaches a solid pharmaceutical preparation with extended release properties, for compound having a very low solubility such as nifedipine and felodipine.

The preparation is obtained by dissolving felodipine or nifedipine in Cremophor® RH 60, and by mixing to the solution carriers such as a mixture containing hydroxypropylcellulose so as to form a hydrophilic gel matrix. The ratio active agent/solubilizer is in the range 1:1 to 1:10. In all the examples of preparations of EP-A-0249587, the active agent is contained into a matrix forming system, especially a gelling matrix.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to a solid preparation suitable for a substantially immediate release of an active agent having a low or very low solubility. For example, the invention relates to a solid preparation for which more than 80 % of the active agent is released within 2 hours, preferably within 1 hour or less from the administration.

The invention has especially as subject matter, a solid preparation obtained by pelletisation, i.e. an agglomeration process whereby fine powders or granules and excipients (non active materials) are shaped into fine, free-flowing spherical or non sperical units. Pellets are defined as dosage forms with a particle size above 250 μm.

The pellet consists of carriers, additives and active ingredients. The carrier can be a natural, a semi-synthetic or a synthetic polymer , but can also be of inorganic origin as for example talc, montmorillonites (as veegum, bentonites, etc...) and other types of clay and phosphates as for example calcium phosphates. The active ingredient is preferably dissolved in a liquid phase (liquid as such or to be liquified by for example shear, temperature, etc...).

As liquid phase, the following ingredient can be described : oils (natural, synthetic, semi-synthetic), polar cosolvents (as polyethylene glycol, glycerol, propyleneglycol), fats and fat substituents and ionic, non ionic tensioactive agents of natural or synthetic origin. The active component can be a drug for human use, a drug for veterinary use, a chemical for application in the agrobusiness (fertilizers, pesticides and analogues), feed additives for human and animal use, etc.

The active ingredient is preferably mixed with the carrier as a solution in order to fix the liquid phase on the carrier. The mixing process of the liquid phase can be performed with different mixing techniques and granulation techniques such as planetary mixers, fluid-bed granulation, high shear mixers, etc. The pellets are then produced via extrusion-spheronisation, fluid-bed technology, rotary granulation, etc...

The carrier can be water soluble or water insoluble and/or insoluble in the gastric medium and has advantageously the form of fine particles, preferably micro particles, for example particles having a diameter size of less than 500 μm.

When mixing the active ingedient and the carrier, or when agglomerating, other additives can be used, said additives having to be non gelling forming agents or having to be in such an amount that they are non gelling forming in water. Such additives can be water soluble or water dispersible.

The invention relates also to the manufacture of a solid dosage form, while the active ingredients are fixed in a liquid phase which is fixed on or in the carrier. An advantage of the invention lays in the preparation of pharmaceutical formulations for human or veterinary application whereby drugs with low solubility

or slow dissolution rate can be formulated into a solid dosage releasing the drug quickly and presenting an enormous advantage in bioavailability. It also allows the handling of drugs and chemicals whereby toxicity and dust formation are providing problems during manipulation; the fixation of active ingredients as a liquid phase on a solid carrier can solve this problem.

The invention presents applications in the pharmaceutical area, food (human & animal) formulation, medicated feed, agrichemical, fixation of oils, fats and fatty substituents in food processing, the transformation of liquid preparations into dry ones, the higher dissolution rate of active ingredients, etc....

The solid preparation of the invention is a solid preparation which contains the active agent dissolved in a solubilizer, said dissolved active agent being contained in particles which are agglomerated in a system which is not a matrix forming system such as a gelling or gel forming system. The system of the invention is not a gel matrix nor a matrix which can form a gel in contact of water.

Preferably, the solubilizer is selected among the group consisting of oils, polar co-solvents, fats, tensioactive agents, solvents, fatty acids, fatty alcohols.

For example, the agglomerated particles or agglomeration of particles is free from compounds which are gel forming in water or in gastric medium or contains such a low amount of such compound that no water gelling effect exists. Compounds which have to be prevented to be used in the agglomeration of particles are for example hydrophylic gelling agent, hydroxypropylmethyl cellulose, compounds for forming an inert matrix,...

The agglomeration contains preferably

essentially micro particles, for example particles with a particle size below 500 μm. The agglomeration of particles contains advantageously more than 40 %, even 50 % by weight micro particles, such as insoluble particles, for example microcrystalline cellulose.

The agglomeration contains, in another embodiment, carboxymethylcellulose, salt thereof such as sodium carboxymethylcellulose or mixture thereof with microcrystalline cellulose.

The active agent is for example selected among the group consisting of hydrochlorothiazide, acetazolamide,acetylsalicylic acid, allopurinol, alprenolol, amiloride, antiarrhythmic, antibiotic, antidiabetic, antiepileptic, anticoagulants, antimycotic, atenolol, bendroflumethiazide, benzbromarone, benzthiazide, betamethasone, ester thereof, bronchodilator, buphenine, bupranolol, chemotherapeutic, chlordiazepoxide, chloroquine, chlorothiazide, chlorpromazine, chlortalidone, clenbuterol, clomipramine, clonidine, co-dergocrine, cortisone, ester thereof, dexamethasone, ester thereof, dextropropoxyphene, diazepam, diazoxide, diclofenac, diclofenamide, digitalisglycoside, dihydralazine, dihydroergotamine, diltiazem, iron salt, ergotamine, ethacrynic acid, ethinylestradiol, ethoxzolamide, fenoterol, fludrocortisone, ester thereof, fluphenazine, furorosemide, gallopamil, guanethidine, hormone, hydrochlorothiazide, hydrocortisone, ester thereof, hydroflumethiazide, immunosuppresive, ibuprofen, imipramine,indomethacine, coronartherapeutic, levodopa, salt of lithium, salt of magnesium, medroxyprogesteron acetate, menadione, methaqualone, 8-methoxypsoralen, methylclothiazide, methyldopa, methylprednisolone, methyltestosterone, methylthiouracil, methylxanthine, metipranolol, molsidomine, morphine, naproxen,

nicergoline, nifedipine, norfenefrine, oxyphenbutazone, papaverine, parmathasone, ester thereof, pentobarbital, perphenazine, phenobarbital, phenylbutazone, phytomenadione, pirenzepine, polythiazide, prazosine, prednisolone, ester thereof, prednisone, ester thereof, probenecid, propranolol, propylthiouracil, rescinnamine, reserpine, secbutabarbital, secobarbital, spironolactone, sulfasalazine, sulfonamide, thioridazine, triamcinolon, ester thereof, triamteren, trichlormethiazide, trifluoperazine, trifluopromazine, tuberculostatic, verapamil, virustatic, zytostatic, bromocriptine, bromopride, carbidopa, carbocromen, quinine, chlorprothixene, cimetidine, clofibrat, cyclizine, desipramine, disulfiram, domperidone, doxepine, fenbufen, flufenamine acid, flunarizine, gemfibrocil, haloperidol, ketoprofen, labetalol, lorazepam, mefenamine acid, melperone, metoclopramide, nortriptyline, noscapine, oxprenolol, oxymetholone, pentazocine, pethidine, stanozolol, sulindac, sulpiride, tiotixen. Other active agents can also been used.

Preferred solubilizers are polyethyleneglycols, polyethyleneglycol derivatives such as esters or ethers, and mixture thereof.

The preparation which is solid has preferably the form of pellets, pellets which, if required, can be provided with a coating, for example an enteric coating. Such a coating is for example a coating disclosed in EP 0217778 (US 4,832,958) or in EP 0153104, the content of which is incorporated by reference for describing examples of coating. While the weight ratio solubilizer/active agent is advantageously greater than 4, it has been observed that by using a ratio higher than 10 an atmost complete release of a drug could be reached in about 5-10 minutes. It has also been

observed that when the weight ratio solubilizer/particles (carrier) was greater than 1:5, preferably 1:4, the release of drug was favorized. It seems that for such ratio the release of drug from the agglomerated particles is increased. Advantageously said ratio is greater than 1:3 or even 1:2.

The invention relates also to a process for the preparation of a solid preparation for a substantially immediate release of an active agent with a low or very low solubility, preparation which contains the active agent dissolved in a solubilizer, said dissolved active agent being contained in particles agglomerated into a system which is not a matrix forming system (such as a gel forming system or a gelling system).

According to a preferred process, the active agent is dissolved or suspended in a solubilizer so as to form a solution or supension, particles are mixed with the solution or supension, and agglomerated particles are formed.

Advantageously, the active agent is dissolved in a solubilizer, the quantity of which is such that the weight ratio solubilizer / active agent is greater than 4, preferably 10.

Preferably, the weight ratio solubilizer/particles is greater than 1:5, preferably greater than 1:4, most preferably 1:3, even 1:2.

The agglomeration of particles is made by means of any suitable liquid which do not contain a sufficient amount of gel forming agent or matrix forming agent and which preferably is free from gel forming agent or matrix forming agent. Such liquid is for example any liquid which can be evaporated after the agglomeration. Said liquid is preferably not the solubilizer of the active agent as such, but may contain

such a solubilizer. Such a liquid can also contain other additives, for example water soluble additives. As typical agglomeration liquid, water can be used, said water being possibly mixed with water soluble additive(s) but non matrix forming and non gel forming and non gelling, water insoluble additives, solubilizer(s) of the active agent.

According to an embodiment of the processes of the invention, before being mixed with the active agent in a dry form or as a solution, the particles or carriers are treated with a solubilizer of the active agent, said solubilizer being or not the solubilizer used for treating the dry mixture particles-active agent or for preparing the solution of active agent. For example, the previously treated particles contain 5 or 10 % solubilizer(s) of the active agent. However, the ratio solubilizer/particles (w/w) is advantageouly greater than 1:5.

As it was observed that very high release of drug could be reached when using such ratio solubilizer/particles, the invention relates also to a mixture of particles, such as water insoluble particles, containing a solubilizer selected among the group consisting of oils, polar co-solvents, fats, tensio-active agents, solvents, fatty acids, fatty alcohols, the weight ratio solubilizer/particles being greater than 1:5, preferably 1:4, most preferably 1:3 or even 1:2.

Advantageously, the particles are micro particles, such microcrystalline cellulose.

Such a mixture is suitable as agent for favorizing the release or bioavailability of an active agent from pellets or from agglomerated particles. The invention relates thus also to the use of such a mixture for the preparation of solid formulation with increased

or improved release or bioavailability of an active agent.

Furthermore, it has been observed that when heating a preparation containing a drug and a suitable solubilizer of said drug, preferably a preparation according to the invention, the bioavailability of the drug was increased and the release of the drug was still increased. For example, such a heat treatment is a treatment at a temperature from 40°C up to the boiling point of the solubilizer, preferably at a temperature from 40°C to 60°C, during at least 3 hours, preferably during at least 24 hours.

DESCRIPTION OF THE DRAWING

Figure 1 shows the dissolution of Nifedipine contained in pellets (1 % Nifedipine - 19 % solubilizer);

Figure 2 shows the dissolution of Indomethacine contained in pellets (2 % Indomethacine - 20 % solubilizer);

Figure 3 shows the dissolution of hydrochlorothiazide contained in pellets containing 3.5 % hydrochlorothiazide and from 2 to 32 % solubilizer (PEG), after preparation (□: 0% solubilizer; + : 2% solubilizer, ◇ : 11% solubilizer; Δ : 21% solubilizer and X : 32% solubilizer);

Figure 4 shows the dissolution of hydrochlorothiazide contained in pellets containing 3.5 % hydrochlorothiazide and from 0 to 21 % solubilizer (Cremophor), after preparation (□ : 0% solubilizer; + : 7% solubilizer; ◇ : 14% solubilizer, and Δ : 21% solubilizer);

Figure 5 shows the dissolution profiles of pellets containing 3.5 % hydrochlorothiazide and 21 % solubilizer (Cremophor) immediately after preparation (□) and after a 6 months storage period at 25° C (+) ;

Figures 6A, 6B and 6C give the X-ray diffraction patterns of respectively pure hydrochlorothiazide, pure microcrystalline cellulose (Avicel PH101) and microcrystalline cellulose pellets containing 3.5 % hydrochlorothiazide, and 32 % solubilizer (PEG 400), and Figures 7A, 7B and 7C give the X-ray diffraction patterns of microcrystalline cellulose pellets containing 3.5 % hydrochlorothiazide and 21 % solubilizer (Cremophor) respectively after preparation, after 6 months storage period at 25°C and after a thermal treatment at 45° C during 96 hours.

DESCRIPTION OF PREPARATIONS

Example 1

5 g Nifedipine has been dissolved in 95 g of a polyethyleneglycol derivative (PEG-7 glyceryl cocoaat sold by Henkel, Düsseldorf, Germany under the trade name CETIOL HE®) at a temperature higher than 40°C, for example 50°C, but at a temperature lower than the boiling point thereof.

When the Nifedipine was completely dissolved the solution was mixed with 375 g water (demineralized) and was then mixed with 375 g microcrystalline cellulose (Avicel PH 101, FMC, Cork, Ireland) in a planetary mixer.

The so obtained mixture was then extruded in an extruder and spheronised in a spheronizer (Model 15, Caleva Ltd., Dorset, U.K.) during 10 minutes at 750 rpm.

Thereafter, the pellets were dried in a fluidized bed dryer at 50°C during 20 minutes so as to obtain pellets having a moisture content of less than 2 %.

The dissolution of the so formed pellets was measured as follows :

1 g pellet sample (diameter size 710-100 μm) was added to 900 ml water having a temperature of 37°C. The mixture was agitated (75 rpm). The method used was conform to the paddle method as described in USP XXII. The extinction was continuously monitored at 3320 nm using a Zeiss PM6-UV spectrophotometer (Zeiss, Oberkochen, Germany).

The dissolution of the pellet is shown in Figure 1. It appears from said figure that more than 50 % of the active ingredient was released within 1 hour.

Example 2

25 g Indomethacine has been dispersed and dissolved in 100 g of a polyethyleneglycol derivative (PEG-7 glyceryl cocoaat sold by Henkel, Düsseldorf, Germany under the trade name CETIOL HE®) at a temperature higher than 40°C, for example 50°C, but at a temperature lower than the boiling point thereof.

400 g water was then added to the indomethacine solution. The so obtained mixture was then mixed with 375 g microcrystalline cellulose (Avicel PH 101, FMC, Cork, Ireland) in a planetary mixer, and then the so obtained mixture was then extruded in an extruder and spheronised in a spheronizer (Model 15, Caleva Ltd., Dorset, U.K.) during 10 minutes at 750 rpm.

Thereafter, the pellets were dried in a fluidized bed dryer at 50°C during 20 minutes so as to obtain pellets having a moisture content of less than 2 %.

The dissolution of 1 g pellet (710-100 μm) was measured as for example 1 and is shown in Figure 2.

It appears from said Figure that about 40 % of the active agent was dissolved within 2 hours.

Examples 3 and 4

Hydrochlorothiazide (HCT) (Batch n° 5327B ; Ludeco, Brussels, Belgium) was used as drug in these examples. This diuretic drug is practically insoluble in water (25°C) and has a solubility of 250 mg/L in 0.1 N HCl (25°C). Polyethylene glycol 400 (PEG 400) (α Pharma, Vichte, Belgium) and PEG 40 hydrogenated castor oil (Cremophor® RH40) (BASF, Ludwigshafen, Germany) were used as solubilising agents. Microcrystalline cellulose (A (A v i c e l ® P H 1 0 1) (FMC Wallington, Little Island, Cork, Ireland) was taken as a filler and the pellet forming material. Demineralised water was used as granulation liquid, next to the solubilising agents.

Pellets containing 2,11,21 and 32 % (w/w) polyethylene glycol 400 and 7,14 and 21 % (w/w) Cremophor® RH40 were prepared. All formulations contained 3.5 % (w/w) of hydrochorothiazide. The remaining part of all formulations consisted of Avicel ® PH101. For each composition the amount of water was adjusted to get the proper plasticity of the mass. A reference formulation was prepared containing 3.5 % (w/w) hydrochlorothiazide and Avicel® PH101 as a filler, without solubilising agent.

Microcrystalline cellulose and hydrochlorothiazide were mixed for 10 minutes at 60 rpm in a planetary mixer (Kenwood Chef, Hampshire, UK). The granulation liquid was prepared by mixing the dissolution enhancer, PEG 400 or the Cremophor® RH40 heated at 45°C, and demineralised water (heated at 45° C in the case of Cremophor® RH40). The Cremophor® RH40/water mixture was cooled to room temperature under continuous stirring. Next, the granulation liquid was added to the powder mix and granulated for 10 minutes at 60 rpm in a planetary mixer

(Kenwood Chef, Hampshire, UK). The granulated mass was extruded at 40 rpm using a basket extruder (Caleva Model 10, Caleva Ltd., Sturminster Newton, Dorset, UK) through a screen with a thickness of 1 mm and die perforations of 1 mm diameter.

135 g of the extrudate was spheronised for 5 minutes at 750 rpm in a Caleva Model 15 spheroniser (Caleva Ltd., Sturminster Newton, Dorset, UK). The resulting pellets were dried for 12 hours in a ventilated oven (Herauws, Obendorf, Germany) at 30° C, after which the dried pellets were sieved using a nest of sieves of 710,1000 and 1400 μm vibrated on a sieve shaker (Rheostat, Willemshaven, Germany) at maximum vibrational speed.

A second preparation method was used for PEG 400 pellets containing 32 % PEG 400 and 3.5 % hydrochlorothiazide (HCT). HCT was first dissolved in the amount of PEG 400 available. This solution was added to the demineralised water, next the complete liquid mixture was added to the microcrystalline cellulose and further processed as in the method described herebefore.

All formulations were stored under ambient conditions during a period of 6 months. Half of the bath formulated with 21 % (w/w) Cremophor® RH40 and 3.5 % (w/w) HCT received a thermal treatment for 96 hours at 45° C.

Dissolution testing was performed on 700 mg pellets (710-1000μm fraction) containing 25 mg hydrochlorothiazide in 0.1N HCl (37° C) using the paddle method (USP XXII) at a rotational speed of 100 rpm. Samples of 5 ml were withdrawn at time t_i (i=0,2,5,10,15,20,30,45,60,75 and 90 minutes) and replaced with an equal amount of test medium. The samples were filtered through a porous metallic filter (pore diameter : 2 μm) and spectrophotometrically analyzed at 273 nm with a ZEISS-spectrophotometer (ZEISS

PMG-UV, Oberkochen, Germany).

Each formulation was tested four times. The percentage of hydrochlorothiazide released from the formulation at time was calculated and corrected for the amount of HCT withdrawn at time t_{i-1}.

After a 6 months storage period under ambient conditions the dissolution tests were repeated in order to check stability of the pellets formulations.

X-ray diffraction patterns were taken of the formulations containing 11 and 32 % (w/w) PEG 400 and the formulations containing 21 % (w/w) Cremophor® RH40 immediately after preparation, after thermal treatment and after 6 months storage under ambient conditions.

During preliminary experiments the maximum amount of PEG 400 that could be incorporated in the Avicel® PH101-pellets was determined to be 43 % (w/w). At this concentration of PEG 400, pellets sticked to each other, whereas below this concentration the pellets still has their typical free-flowing capacity. The limit of Cremophor® RH40 concentration that could be incorporated in the pellets was 21 % (w/w). Increasing the concentration of Cremophor® RH40 in the pellets caused the hardness of the pellets to drop below an acceptable level.

The in-vitro dissolution profiles of the formulations containing PEG 400 are shown in figure 3. Pellets containing 21 and 32 % (w/w) PEG 400 released more than 70 and 80 % of the active ingredient within the first 5 minutes, respectively. This means a drastic increase in the in-vitro release rate compared to the reference pellets releasing 10 and 45 % of HCT after 5 and 90 minutes, respectively. No differences between the in-vitro dissolution profiles were obtained from pellets prepared by both methods. The typical X-ray diffraction pattern of crystalline HCT in the pellets containing

32 % (w/w) PEG 400 could not be detected (Fig. 6) showing that the drug was dissolved and said dissolved drug was contained in microcrystalline cellulose. When reducing the percentage of PEG 400 in the formulation to 11 and 2 % (w/w), the in-vitro drug release rate was lowered to 26 % and 11 % after 5 minutes, respectively (Fig 3). The in-vitro release rate of HCT from the formulation containing 2 % (w/w) PEG 400 was very similar to the reference pellets. A solubility test of HCT in PEG 400 at room temperature showed that only a fraction of the amount HCT present could dissolve in the 2 % PEG 400 formulation. Although the solubility test showed that all the HCT could dissolve in the PEG 400 present in the formulation containing 11 % (w/w) PEG 400, the in-vitro release rate however dropped compared to the formulation containing 21 % (w/w) PEG 400. The X-ray diffraction patterns of the pellets containing 11 % of PEG 400 showed no difference with the patterns of the pellets containing 32 % of PEG 400 (Fig.6) indicating that all HCT was dissolved in PEG 400. This shows clearly that the solubilizer has an influence on the microcrystalline cellulose particle, i.e. that when using sufficient solubilizer, the solubilizer increases the release of the drug. This clearly shows that the use of particles containing solubilizer, for example only solubilizer, increase the release of the drug and act as agent for increasing the release or bioavailability of the drug.

Storage of the PEG 400-pellets under ambient conditions for a period of 6 months did not alter the dissolution profile of HCT.

Figure 4 shows the dissolution profiles of the pellets containing 0,7,14 and 21 % (w/w) Cremophor® RH40. An increase in the in-vitro release rate of HCT from the Avicel® PH101-pellets was seen, although not as

pronounced compared to the use of 32 % (w/w) PEG 400. The X-ray diffraction pattern of the formulation containing 21 % (w/w) of Cremophor® RH40 showed the presence of some HCT-crystals in the formulation (Fig. 7), indicating that only part of the HCT was in solubilized form in the pellets. The dissolution profiles of pellets containing 21 % of Cremophor® RH40 showed an increase of the in-vitro release rate after storage under ambient conditions (25°C) during a time period of 6 months (Fig. 5). The same increase of the in-vitro release rate was seen after the thermal treatment of the pellets at 45°C for 96 hours. This increase is due to an increase of the amount of HCT solubilised in the Cremophor® RH40. This hypothesis was confirmed by X-ray diffraction patterns showing that no crystalline HCT could be detected after a storage period of 6 months under ambient conditions (25° C) (Fig. 7B), nor after a thermal treatment at 45° C during 96 hours (Fig. 7C). Although all HCT was solubilised in Cremophor® RH40 the release rate of HCT did not reach the release rate of the pellets formulated with 32 % (w/w) PEG 400.

Example 5

2,5 g alprenolol and 10 g hydrochlorothiazide have been dry mixed for 10 minutes at 60 rpm in a planetary mixer (Kenwood Chef, Hampshire, UK).

The mixture has then been mixed with 50 g PEG-800 at 50° C so as to obtain a solution of alprenolol and hydrochlorothiazide.

95 g water was then added to the solution and the so obtained solution was mixed with 125 g microcrystalline cellulose (Avicel PH 101) in a planetary mixer.

The mixture was then extruded, spheronized and

dried as described in example 1.

Example 6

6.1 Preparation of granules of microcrystalline cellulose and PEG-400

A granulation liquid was prepared by mixing 100 g polyethyleneglycol (PEG-7 glyceryl cocoaat - CETIOL HE®) and 375 g water.

375 g microcrystalline cellulose Avicel PH 101 was mixed with the granulation liquid and granulated for 10 minutes at 60 rpm in a planetary mixer (Kenwood Chef, Hampshire, UK).

6.2 Preparation of granules of microcrystalline cellulose, lactose, PEG-400 and HCT

A solution has been prepared by mixing 100 g PEG-400 (CETIOL HE®), 10 g lactose, 20 g HCT and 375 g water.

300 g microcrystalline cellulose Avicel PH 101 was mixed with the above mentioned solution, and granulated as explained in point 6.1.

6.3 Preparation of pellets

100 g of granules of Avicel-PEG 400 were mixed with 200 g of granules of Avicel-HCT-PEG 400. The mixture was extruded at 40 rpm using a basket extruder (Caleva Model 10, Caleva Ltd., Sturminster Newton, Dorset, UK) through a screen with a thickness of 1 mm diameter. The extrudate was then spheronized for 5 minutes at 750 rpm in a Caleva Model 15 spheronizer and the resulting pellets were dried for 12 hours in a ventilated oven at 30° C.

The pellets contained :

2.5 % HCT

1.2 % Lactose

74 % Avicel (microcrystalline cellulose)

22.3 % PEG-400

6.4 Pellets were prepared by using only granules of the preparation 6.2

The so obtained pellets had a good release of drug in water, however said release was no so excellent as the release of the pellets of the preparation 6.3.

Example 7

Pellets containing 3.5 % Hydrochlorothiazide (HCT) and 30 % Polyethylene glycol PEG 400 have been prepared as follows :

A solution of hydrochlorothiazide has been prepared by mixing 35 g HCT with 150 g PEG 400 and 300 g water at 50° C.

675 g of microcrystalline cellulose Avicel PH101 was mixed with 150 g PEG 400 in a planetary mixer for 10 minutes. Particles containing PEG 400 were so obtained.

The so obtained particles were then mixed with the solution of HCT in a planetary mixer so as to obtain a granulated mass. Said mass was then transformed into pellets in a manner similar to that disclosed for examples 3 and 4.

A previous treatment of the carrier with the solubilizer seems to be suitable for having an excellent release, showing a further possible use of the mixture particles according to the invention.

Example 8

Pellets containing 3.5 % hydrochlorothiazide, 23 % Polyethylene glycol PEG 400 and 10 % Cremophor RH40 have been prepared as follows :

A solution of hydrochlorothiazide has been prepared by mixing 35 g HCT with 150 g Cremophor RH 40 and 80 g PEG 400 in a planetary mixer for 10 minutes. Particles containing Cremophor RH 40 and PEG 400 were so

obtained.

The so obtained particles were then mixed with the solution of HCT in a planetary mixer so as to obtain a granulated mass. Said mass was then transformed into pellets in a manner similar to that disclosed for examples 3 and 4.

Example 9

Pellets containing various active agents have been prepared as described in example 1, but by using various amounts of water "W", microcrystalline cellulose (Avicel PH 101) "MC", and "PEG" (Cetiol HE) or/and Cremophor RH40 "C". Said amounts are given in the following table.

TABLE

ACTIVE AGENT	W	MC	C	PEG
5g Nifedipine	375g	375g	0g	150g
5g Nifedipine	375g	300g	75g	25g
10g Ibuprofen	375g	300g	0g	100g
10g Diclofenac	375g	300g	0g	100g
5g Cimetidine	275g	0g	100g	0g

CLAIMS

1. A solid preparation for a substantially immediate release of an active agent with low or very low solubility, which contains the active agent dissolved in a solubilizer, said dissolved active agent being contained in solid particles which are agglomerated into a system of agglomerated particles which is not a matrix forming system.

2. The preparation of claim 1, in which the solubilizer is selected among the group consisting of oils, polar co-solvents, fats, tensio-active agents, solvents, fatty acids, fatty alcohols.

3. The preparation of claim 1, in which the system of agglomerated particles is free from compounds which are gel forming in water.

4. The preparation of claim 1, in which the system of agglomerated particles contains micro particles.

5. The preparation of claim 1, in which the system of agglomerated particles contains more than 50 % by weight of micro particles, preferably micro-crystalline cellulose and/or sodium carboxy-methylcellulose.

6. The preparation of claim 1, in which the active agent is selected from the group consisting of hydrochlorothiazide, acetazolamide,acetylsalicylic acid, allopurinol, alprenolol, amiloride, antiarrhythmic, antibiotic, antidiabetic, antiepileptic, anticoagulants,

antimycotic, atenolol, bendroflumethiazide, benzbromarone, benzthiazide, betamethasone, ester thereof, bronchodilator, buphenine, bupranolol, chemotherapeutic, chlordiazepoxide, chloroquine, chlorothiazide, chlorpromazine, chlortalidone, clenbuterol, clomipramine, clonidine, co-dergocrine, cortisone, ester thereof, dexamethasone, ester thereof, dextropropoxyphene, diazepam, diazoxide, diclofenac, diclofenamide, digitalisglycoside, dihydralazine, dihydroergotamine, diltiazem, iron salt, ergotamine, ethacrynic acid, ethinylestradiol, ethoxzolamide, fenoterol, fludrocortisone, ester thereof, fluphenazine, furorosemide, gallopamil, guanethidine, hormone, hydrochlorothiazide, hydrocortisone, ester thereof, hydroflumethiazide, immunosuppresive, ibuprofen, imipramine,indomethacine, coronartherapeutic, levodopa, salt of lithium, salt of magnesium, medroxyprogesteron acetate, menadione, methaqualone, 8-methoxypsoralen, methylclothiazide, methyldopa, methylprednisolone, methyltestosterone, methylthiouracil, methylxanthine, metipranolol, molsidomin, morphine, naproxen, nicergoline, nifedipine, norfenefrine, oxyphenbutazone, papaverine, parmathasone, ester thereof, pentobarbital, perphenazine, phenobarbital, phenylbutazone, phytomenadione, pirenzepine, polythiazide, prazosine, prednisolone, ester thereof, prednisone, ester thereof, probenecid, propranolol, propylthiouracil, rescinnamine, reserpine, secbutabarbital, secobarbital, spironolactone, sulfasalazine, sulfonamide, thioridazine, triamcinolon, ester thereof, triamteren, trichlormethiazide, trifluoperazine, trifluopromazine, tuberculostatic, verapamil, virustacic, zytostatic, bromocriptine, bromopride, carbidopa, carbocromen, quinine, chlorprothixene, cimetidine, clofibrat, cyclizine, desipramine, disulfiram, domperidone,

doxepine, fenbufen, flufenamine acid, flunarizine, gemfibrocil, haloperidol, ketoprofen, labetalol, lorazepam, mefenamine acid, melperone, metoclopramide, nortriptyline, noscapine, oxprenolol, oxymetholone, pentazocine, pethidine, stanozolol, sulindac, sulpiride, tiotixen.

7. The preparation of claim 1, in which the solubilizer is a polyethyleneglycol, a polyethylene-glycol derivative or a mixture thereof.

8. The preparation of claim 1, which is provided with an enteric coating.

9. The preparation of claim 1, in which the weight ratio solubilizer/active agent is at least 4, preferably greater than 10.

10. The preparation of claim 1, in which the weight ratio solubilizer/particles is greater than 1:5, preferably 1:4.

11. The preparation of claim 1, in which the weight ratio solubilizer/particles is greater than 1:3, preferably 1:2.

12. Process for the preparation of a solid preparation for a substantially immediate release of an active agent with a low or very low solubility, preparation which contains the active agent dissolved in a solubilizer, said dissolved active agent being contained into solid particles agglomerated in a system, which is not a matrix or gelling forming system, in which :

* the active agent is dissolved or suspended in a

solubilizer so as to form a solution or suspension,

* solid particles, possibly pretreated with a solubilizer of the active agent, are mixed with the solution or suspension, and
* the particles are agglomerated without gelling forming agent

or in which :

* solid particles possibly pretreated with a solubilizer of the active agent and the active agent in powder form are mixed together,
* the so obtained mixture is mixed with solubilizer of the active agent, and
* the particles are agglomerated without gelling forming agent.

13. Process of claim 12, in which the active agent is dissolved in a solubilizer, the quantity of which is such that the weight ratio solubilizer / active agent is greater than 4, preferably than 10.

14. Process of claim 12, in which the solubilizer is selected among the group consisting of oils, polar co-solvents, fats, tensio-active agents, solvents, fatty acids, fatty alcohols.

15. Process of claim 12, in which the weight ratio solubilizer/particles is greater than 1:5, preferably greater than 1:4.

16. Process of claim 12, in which the weight ratio solubilizer/particles is greater than 1:3, preferably greater than 1:2.

17. Process of claim 12, in which after the agglomeration of the particles, and possibly the drying

thereof, the preparation is heated at a temperature higher than 40°C during at least 3 hours.

18. Mixture of particles containing a solubilizer selected among the group consisting of oils, polar co-solvents, fats, tensio-active agents, solvents, fatty acids, fatty alcohols, the weight ratio solubilizer-/particles being greater than 1:5, preferably 1:4.

19. Mixture of particles of claim 18, in which the solubilizer is selcted among polyethyleneglycols and polyethyleneglycol derivatives, mixture thereof.

20. Mixture of claim 18 or 19, in which the particles are micro particles, preferably microcrystalline or water insoluble particles.

21. Mixture of claim 18 or 19, in which the weight ratio solubilizer/particles is greater than 1:3, preferably 1:2.

22. Mixture of claim 18 or 19, which has the form of particles agglomerated.

23. Agent for increasing the release or bioavailability of an active agent, in which the agent for increasing the release or bioavailability comprises a mixture according to one of the claims 18 to 21.

24. Use of a mixture according to one of the claims 18 to 21 for preparing solid preparation formulation with increased release or bioavailability of an active agent.

25. Process for increasing the bioavailability of solid preparation containing a solubilizer and an active agent, in which the preparation is heated at a temperature higher than 40°C during at least 3 hours.

FIG. 1

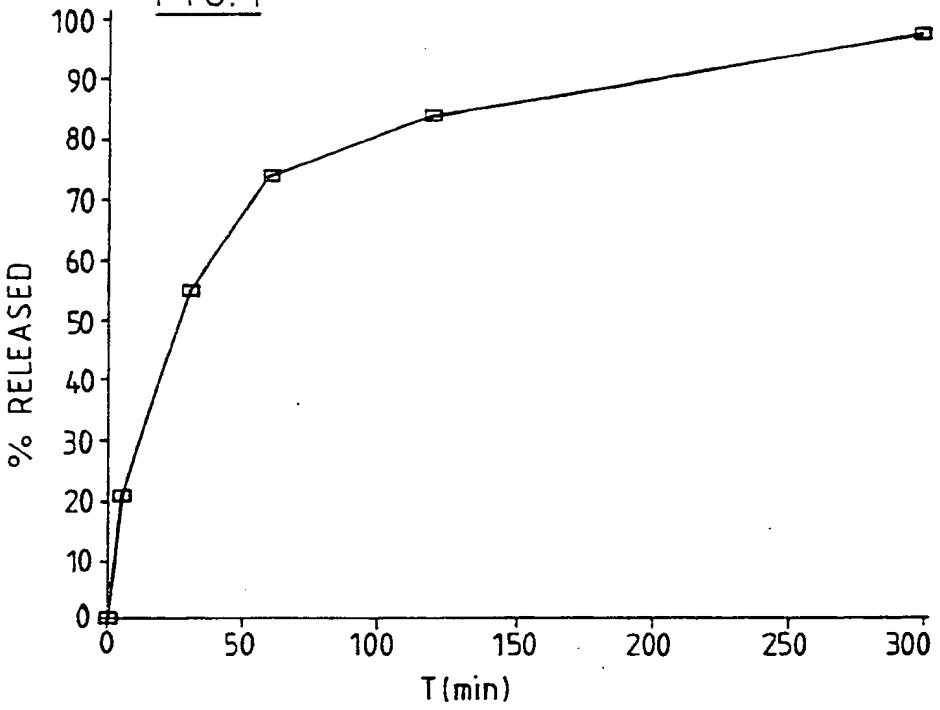
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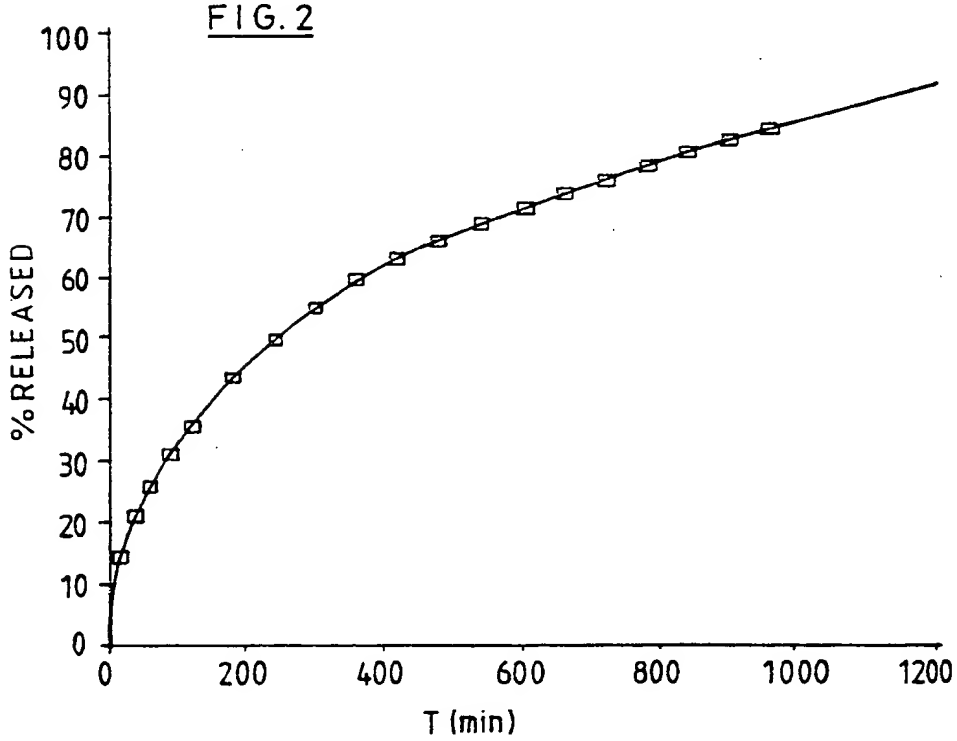
FIG. 2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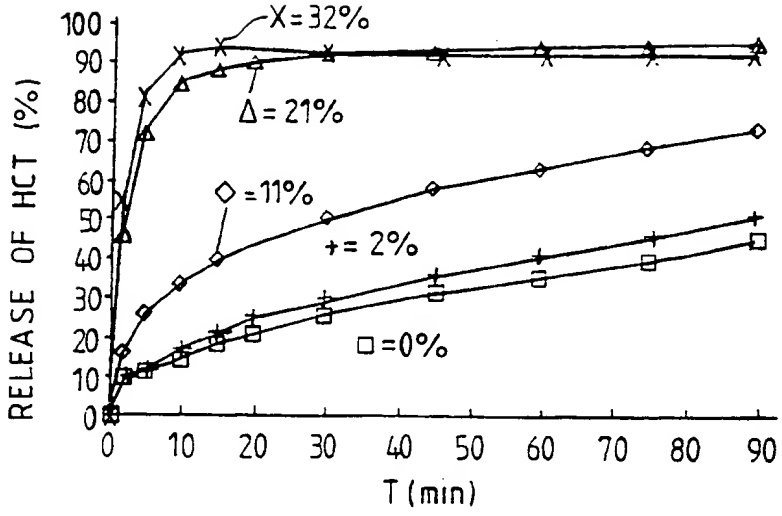


FIG. 3

FIG. 4

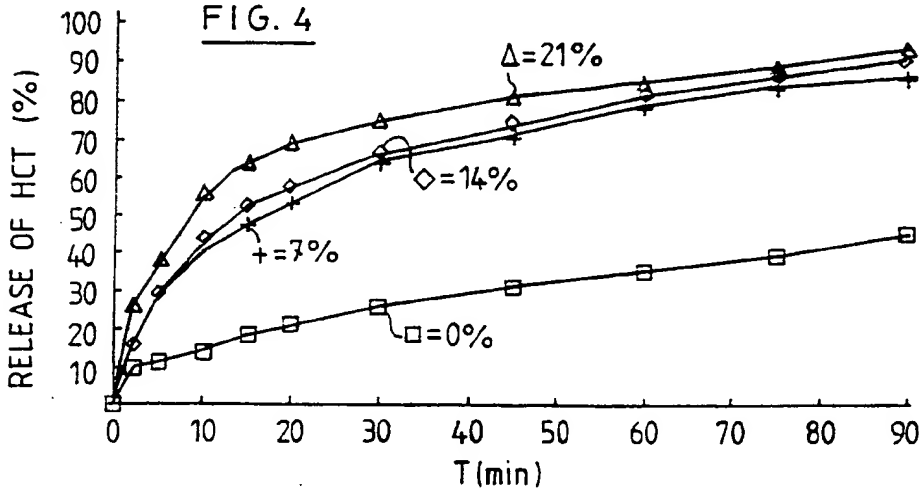
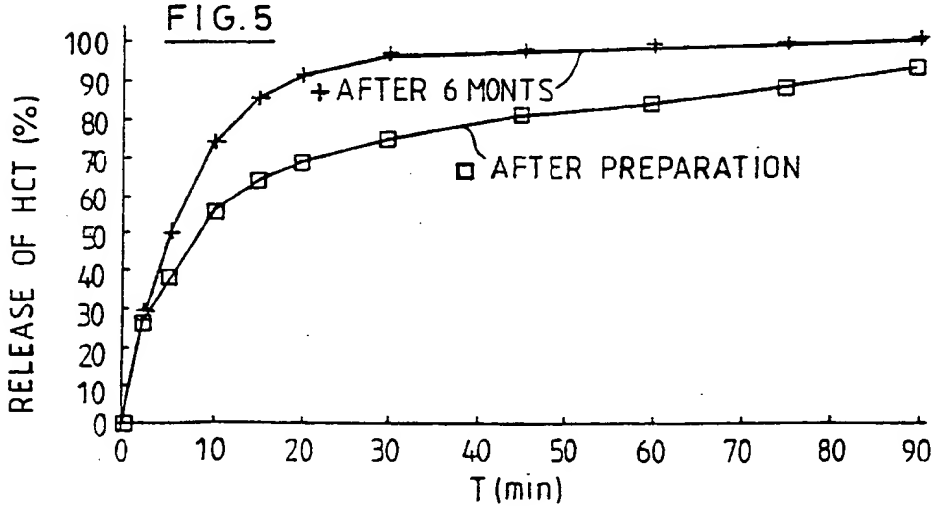


FIG. 5



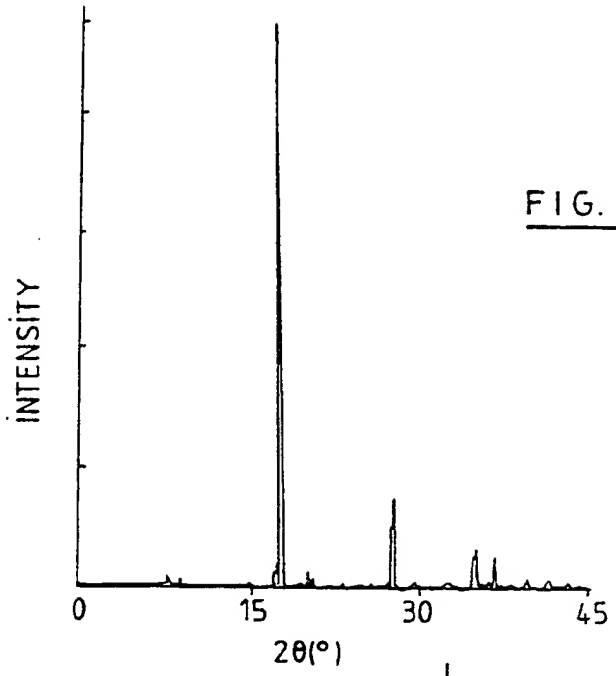


FIG. 6A

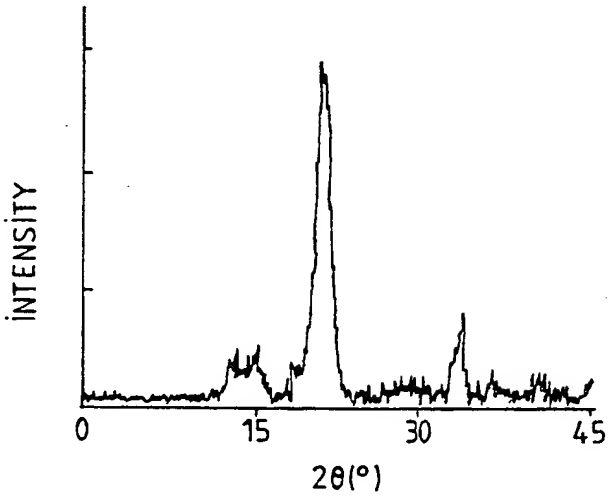


FIG. 6B

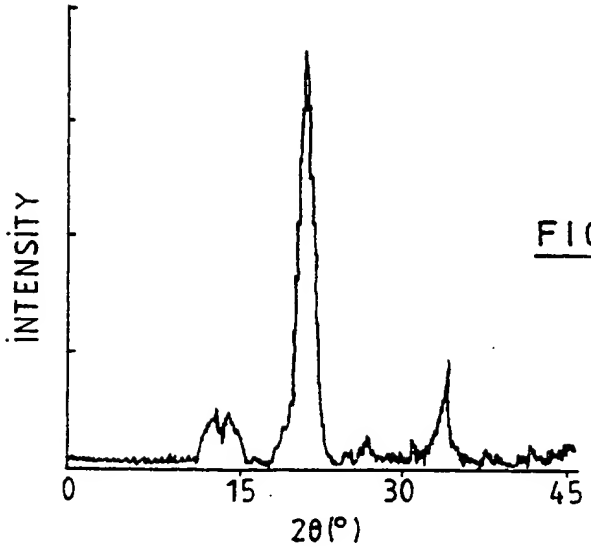


FIG. 6C

FIG.7A

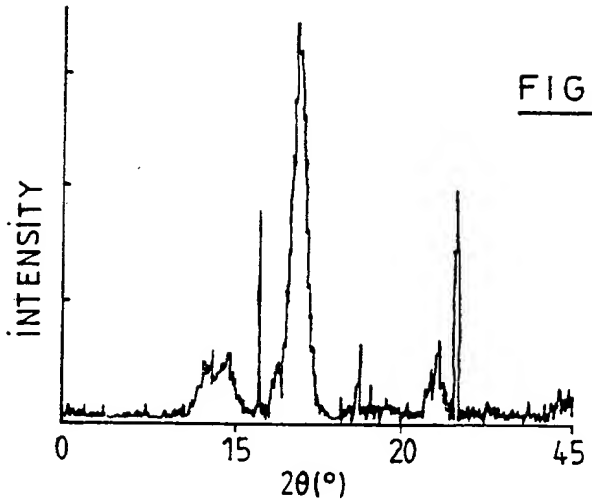


FIG. 7B

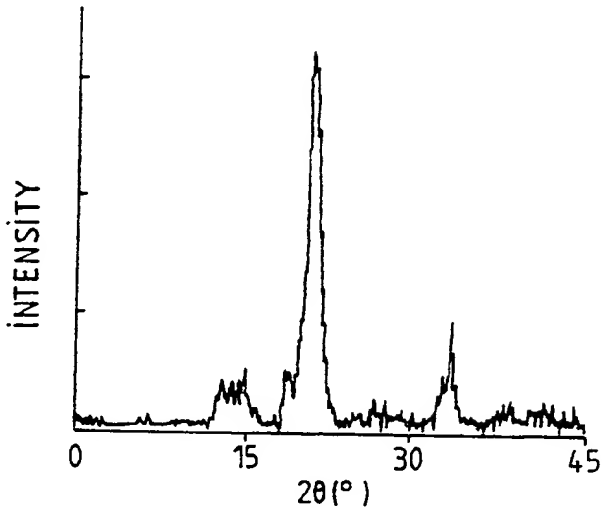
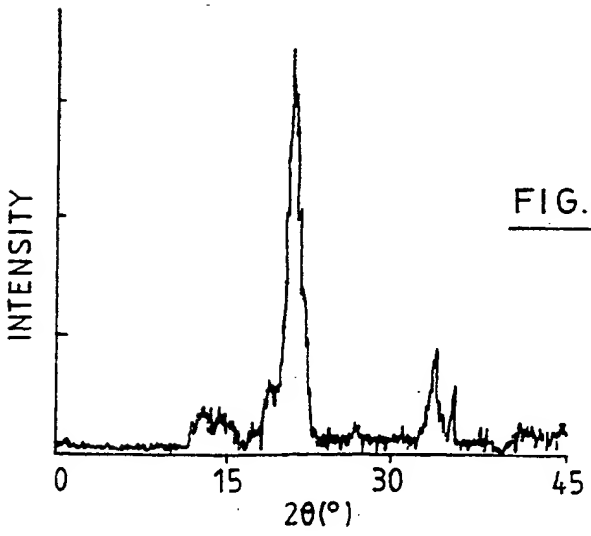


FIG.7C



INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/BE 94/00029

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 204 596 (RHONE POULENC SANTE) 10 December 1986 see column 1, line 32 - column 2, line 52 see column 4, line 22 - line 23 see page 4 - page 5; examples 1-17 ---	1-25
X	GB,A,1 148 802 (EASTMANN KODAK COMPANY) 16 April 1969 see page 2 - page 3; examples ---	12,15, 16,18, 20-22
A	EP,A,0 537 070 (TERUMO K.K.) 14 April 1993 see page 12; example 3 ---	1-25
X	EP,A,0 249 587 (AKTIEBOLAGET HASSLE) 16 December 1987 cited in the application see page 4 - page 5; example 3 --- -/--	12-16, 18,20-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1994	29. 07. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Boulois, D

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/BE 94/00029

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 00093 (BIOVAIL RESEARCH CORPORATION) 7 January 1993 see page 13; example 2	12, 15-18, 20-22,25
A	GB,A,1 367 608 (BIOLOGICAL CONCEPTS INC) 18 September 1974 see page 7; example 4	1-25
A	US,A,3 146 167 (RUSSEL J.L. JR ET AL) 25 August 1964 see column 5; example 2	1-25
A	US,A,3 655 864 (GRASS G.M. ET AL) 11 April 1972 cited in the application see column 5, line 14 - line 38	1-25
X	DATABASE WPI Week 8804, Derwent Publications Ltd., London, GB; AN 88-021903 & DD,A,249 186 (LUTHER UNIV. HALLE) 2 September 1987 see abstract	1-7,12, 14,23,24
X	EP,A,0 310 999 (MERREL DOW PHARMACEUTICALS INC) 12 April 1989 see page 6 - page 7; example 2 see claims 1,8	1-8,10, 11,18-24
X	US,A,RE33963 (HEGASY A.) 16 June 1992 see column 6; example 6	1-6, 10-12, 14-16, 18,20-24
X	US,A,5 169 645 (SHUKLA A.J. ET AL) 8 December 1992 see column 5 - column 6; example 5	12-14
A	EP,A,0 387 782 (EGIS GYOSGYSZERGYAR) 19 September 1990 see page 7; example 4	1-25
A	EP,A,0 217 778 (PHARLYSE S.A.) 8 April 1987 see page 7; example 2	1-25

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/BE 94/00029

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0204596	10-12-86	FR-A-	2581541	14-11-86
		AU-B-	579012	10-11-88
		AU-A-	5722486	13-11-86
		CA-A-	1266841	20-03-90
		JP-A-	61260029	18-11-86
GB-A-1148802		NONE		
EP-A-0537070	14-04-93	JP-A-	5097672	20-04-93
		AU-B-	637549	27-05-93
		CA-A-	2079938	09-04-93
EP-A-0249587	16-12-87	AU-B-	602677	25-10-90
		AU-A-	7004387	15-10-87
		CA-A-	1304294	30-06-92
		DE-A-	3779183	25-06-92
		FI-B-	91826	13-05-94
		JP-A-	62242613	23-10-87
		SU-A-	1743332	23-06-92
		US-A-	4803081	07-02-89
WO-A-9300093	07-01-93	US-A-	5288505	22-02-94
		AU-A-	2243092	25-01-93
		CA-A-	2111085	07-01-93
		EP-A-	0591424	13-04-94
GB-A-1367608	18-09-74	FR-A,B	2226992	22-11-74
US-A-3146167		NONE		
US-A-3655864	11-04-72	AU-B-	462444	26-06-75
		AU-A-	3369071	29-03-73
		GB-A-	1306018	07-02-73
EP-A-0310999	12-04-89	AU-A-	2346088	10-08-89
		CA-A-	1316458	20-04-93
		DE-A-	3873011	27-08-92
		JP-A-	1128924	22-05-89
		US-A-	4929605	29-05-90

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intel. ional Application No
PCT/BE 94/00029

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-RE33963	16-06-92	DE-A-	3142853	11-05-83
		DE-A-	3205399	25-08-83
		CA-A-	1184118	19-03-85
		EP-A,B	0078430	11-05-83
		JP-C-	1684800	31-07-92
		JP-B-	3038248	10-06-91
		JP-A-	58083617	19-05-83
		JP-A-	62228017	06-10-87
		US-A-	4892730	09-01-90
		US-A-	4981683	01-01-91
		US-A-	4882144	21-11-89
US-A-5169645	08-12-92	NONE		
EP-A-0387782	19-09-90	CA-A-	2012194	14-09-90
		CH-A-	680416	31-08-92
		FR-A-	2644343	21-09-90
		GB-A,B	2229095	19-09-90
		JP-A-	2279626	15-11-90
		US-A-	5108757	28-04-92
EP-A-0217778	08-04-87	LU-A-	86099	02-04-87
		DE-A-	3685392	25-06-92
		US-A-	4832958	23-05-89